



# Chronic *Aspergillus fumigatus* colonization of respiratory tract in Cystic Fibrosis: Diagnosis, management and antifungal resistance in a French cohort of CF patients

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**Introduction:**

Cystic fibrosis (CF) is the major genetic inherited disease in the European Caucasian population, with an average of 1 in 3000 living births in France. Prognosis depends essentially on the lung impairments. While considerable attention therefore has been paid over recent decades to prevent and treat bacterial respiratory infections, we observed emergence of fungi colonization in CF respiratory tract. In particular, *Aspergillus fumigatus* represents the most common causative agent colonizing the airways of CF patients; it can be responsible for Allergic Bronchopulmonary Aspergillosis (ABPA). Since oral corticosteroids and itraconazole represent the mainstay of ABPA treatment, long-term therapy may increase the risk of acquired resistance to azoles that is mainly associated with amino acid substitutions in the CYP51A gene of *A. fumigatus*.

**Objective:**

Because CF patients are chronically exposed to itraconazole, our study aimed to evaluate the prevalence of azole resistance in isolates prospectively collected from CF patients followed-up in seven French hospitals involved in our national prospective study ("MucoFong" study – PHRC1902). To our knowledge, it is the first multicenter study focused on azole resistance of *A. fumigatus* in CF.

**Methods:**

A total of 87 isolates of *A. fumigatus* was collected in 85 patients. The MICs of azole drugs were evaluated for each isolate using the E-test® strips. Isolates were characterized at the molecular level by targeting ITS,  $\beta$ -tubulin and MAT-A/a genes. The *cyp51A* gene as well as its promoter was sequenced.

**Results and Discussion:**

A majority of isolates (88.1%) were found sensitive to itraconazole (MIC 2 mg/ml), and 2 new mutations were identified and localized within 3-dimensional Cyp51A protein model. To obtain insight into azole resistance of *A. fumigatus*, the results are analyzed taking into account clinical data, itraconazole exposition, and the potential correlation between the identified CYP51A mutations and azole resistance is discussed based on the Cyp51A protein homology model.

**Titre abrégé :** Chronic *Aspergillus fumigatus* colonisation of respiratory tract in cystic fibrosis: diagnosis, management and antifungal resistance in a French cohort of cystic fibrosis patients

Résumé en anglais

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